PATHOLOGY OF MYATONIA CONGENITA (OPPENHEIM)

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Complete postmortems in cases of this condition have been reported by Spiller, Baudouin, Lereboullet-Baudouin, Collier-Holmes, Rothmann, Beevor and Kaumheimer; Reyher-Helmholz in one necropsy examined only the musculature, and Bing, Collier-Holmes and Skoog respectively, examined a small piece of muscle excised from the patient during life.

The scarcity of the anatomic examinations recorded, especially in the American literature, the only reports given being those by Spiller-Smith and Skoog, justifies the publication here of the results of the examination of pieces of muscle and nerve in the case of myatonia congenita, which I reported in the AMERICAN JOURNAL OF DISEASES OF CHILDREN, October, 1914.

Sept. 8, 1914, the baby spoken of in that report became cyanotic while nursing and died suddenly, about one week after my last visit. A necropsy to examine the entire nervous system and the organs of inner secretion and to establish the cause of the sudden death (thymus, bronchitis?), was refused and I had to content myself with the excision of a large piece of the calf musculature throughout its depth, and of the peroneal and popliteal (tibial) nerves of the right leg, two hours after death.

The subcutaneous fat-tissue over the gastrocnemius muscle was about 8 mm. thick. The musculature was markedly pale pink, but apparently of undiminished volume. The specimens were preserved in a 10 per cent. formaldehyd solution and later were examined by Dr. Maximilian Herzog, pathologist of the Cook County Hospital, to whom I am indebted for the following report:

From the muscle removed pieces were embedded in paraffin, sectioned and stained with hematoxylin-eosin. The sections reveal a very advanced and marked condition of atrophy of muscular tissue (Fig. 1). The individual bundles of muscle fibers are small and separated from each other by a large amount of areolar fatty tissue. The latter presents the usual appearance of fat cells. It appears that from one-third to one-half of the entire original muscle tissue is now composed of areolar tissue. The latter appears to be quite vascular. Examination even under low power already shows enormous increase of sarcolemma-nuclei.

Under oil-immersion magnification it is seen that the muscle fibers left do not show well the normal striation; it is particularly the longitudinal striation

which is indistinct. On the other hand, the transverse striation in some places at least, is unusually distinct and it appears that the dark lines between the disks are widened (Fig. 2).

The muscle fibers are in cross-sections narrow, round or oval and vary in size (Fig. 3). No hypertrophic fibers are present. The vessels in the interstitial and areolar connective tissue appear to be numerically increased and perhaps enlarged in size, but there is no marked thickening of their walls. The sarcoplasma-nuclei under the high power show oval or round with a considerable amount of chromatic substance. In some places indications of karyokinetic figures can be seen. It is very evident that the great numbers of sarcolemma-nuclei and the karyokinetic figures indicate an attempt at regeneration or new formation. Of the sarcolemma-nuclei which are so numerously found in the

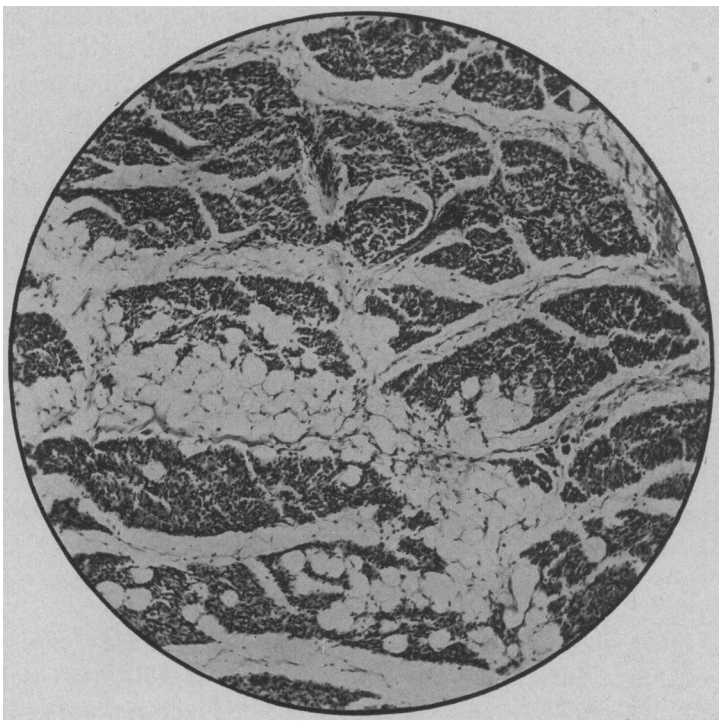

Fig. 1.—Muscle bundles small, separated by proliferated connective and by areolar fatty tissue; enormous increase of the number of sarcolemma-nuclei. From microphotograph, x 60.

sections, the majority have retained their normal relation directly under the sarcolemma itself, but here and there one sees places in the sections where the nuclei are found in the sarcoplasm itself, even in its very center. This of course is the condition which we generally see in regenerating voluntary muscle fibers. The development of the muscle appears to be retarded, presenting a prenatal stage, the not developed fibers being replaced by areolar tissue.

Peripheral nerves stained by Weigert's method, show marked, but not very profound degenerative changes. On the whole the myelin sheath is well preserved, but here and there it is thinned out and reduced to a very thin mantle of the axis-cylinder. One also occasionally sees breaks in the myelin sheath and the interspaces at the nodes of Ranvier are increased in size. There has

not been much proliferation of neurilemma nuclei, but the ordinary connective tissue between the individual bundles of nerve fibers is very much increased, so that the peroneal nerve contains more fibrous connective tissue than nerve tissue proper (Fig. 4).

Correlating the clinical findings with the pathologic findings described above, the profound atrophy and the decreased number of the muscle fibers explain the paralysis; the intense proliferation of the connective and fatty tissue, infiltrating and replacing the muscle substance, made the muscle appear of normal volume and concealed the

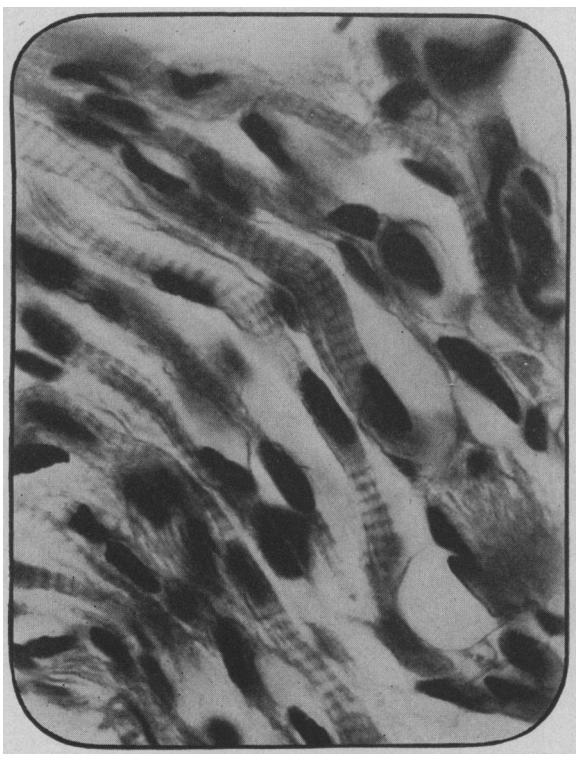

Fig. 2.—Transverse striation unusually distinct; atrophic fibers; no hypertrophic fibers. From microphotograph, x 1,000.

actual atrophy; the flabbiness of the musculature and the striking impossibility of distinguishing the muscle from the panniculus adiposus by palpation, as reported in the clinical history of the case, are the result of the same pathologic condition.

MUSCLE AND NERVE FINDINGS AS RECORDED IN LITERATURE

To gain a more comprehensive picture of the various findings in the muscles and the nervous system in this condition, so far as known, it is necessary briefly to review the literature on this subject.

In Spiller's case the muscles amid a hypertrophic interfibrillary and fatty tissue were little developed; the fibers were hyaline and very small; their longitudinal striation was indistinct, the number of the nuclei of the connective tissue considerably increased. The nervous system was intact.

Bing observed in a very small piece of muscle, excised from a 3½ year old child, only a certain increase of the number of the nuclei.

Skoog noted a great diminution in the size of all muscle fibers, their diameters measuring from 8 to 12 microns; their myoplasma in many

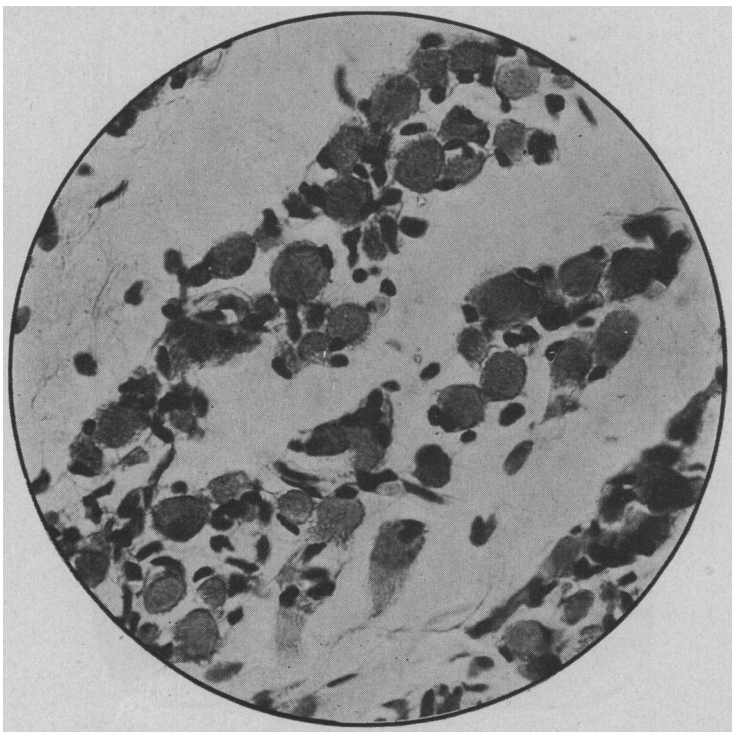

Fig. 3.—Atrophic muscle fibers of various diameter; fibers separated by proliferation of connective and fatty tissue. From microphotograph, x 450.

places had undergone a complete degeneration and replacement with adipose or connective tissue. There was, moreover, much fatty tissue between the individual bundles, a very marked proliferation of the sarcolemma nuclei and a pronounced thickening of the walls of the vessels, including the capillaries.

While in these cases, including my own, only atrophic fibers were found, other authors, as Reyher-Helmholz and Collier-Holmes have observed, in addition, hypertrophic fibers in such numbers that the

microscopic pictures resembled more the ordinary findings of progressive muscular dystrophy.

Reyher-Helmholz noted that some of the muscles of their patient, especially those of the lower extremities, were much affected. The fibers—of which some were slender, some hypertrophied—were scanty and interrupted by adipose and connective tissue which abounded in nuclei; also the transverse striation was indistinct or entirely absent. Unfortunately the central nervous system was not examined to

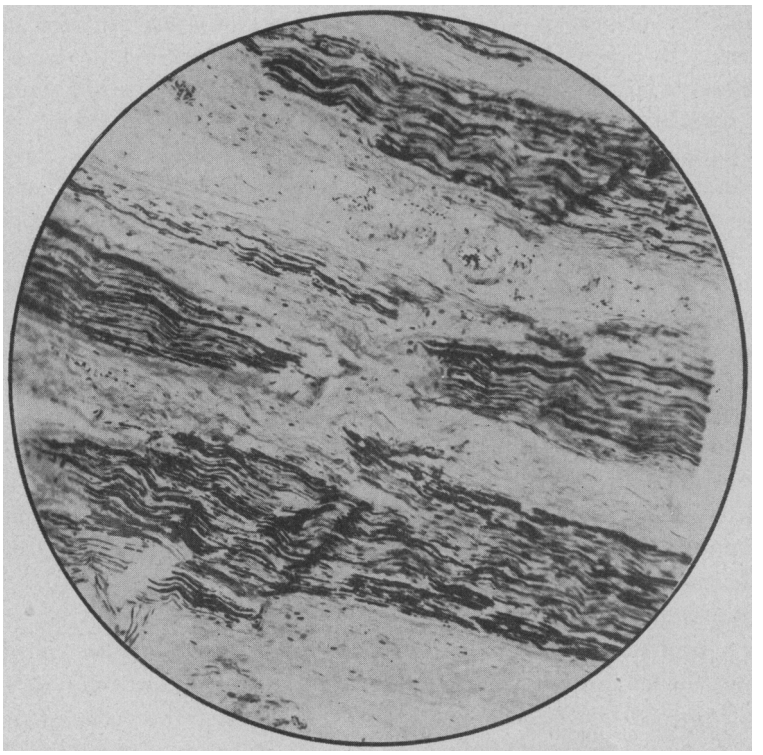

Fig. 4.—Peripheral nerve, stained by Weigert's method. Marked increase of fibrous connective tissue between the nerve bundles. From microphotograph, x 65.

determine whether these changes were primary in the muscles themselves or secondary to an affection of the anterior horns of the spinal cord.

Collier-Holmes, having excised a piece of the hamstring muscle (in Case 2) under general anesthesia, noted that macroscopically it was markedly pale and very much infiltrated by fat tissue. Microscopically only a few fiber bundles were found to be normal; a great number of the fibers were extremely small, with an average diameter

of from 6 to 12 microns; their contour was irregular, being principally oval or round, and never presenting the normal polygonal or facetted appearance of cross-sections. These small fibers, when cut longitudinally, however, appeared of fairly uniform caliber and had a well-preserved cross striation. In some of these there was marked proliferation of the sarcolemma nuclei. Very striking indeed was the presence of numerous enormous fibers with diameters of from 100 to 150 microns. These giant fibers here and there presented regressive changes; some of them contained central nuclei either embedded in normal myoplasma or surrounded by a zone of undifferentiated sarcoplasma. In other fibers the regressive changes had led to vacuolization and a splitting up, or the more or less disintegrated myoplasma was invaded by the sarcoplasm and sarcoplastic nuclei. The connective tissue was greatly increased and in places even penetrated between the individual muscle fibers. There was also a notable amount of loose adipose tissue between the muscle bundles. The muscle spindles on the whole proved to be normal, but in places their sheaths appeared slightly thickened. Considerable thickening of the walls of many blood vessels was noticeable. In the muscles were remarkably few myelinated nerves and the myelin sheaths seemed poorly developed. In Case 1 (complete necropsy) the muscles presented lesions similar to those just described.

The myelin sheaths of the peripheral nerves were imperfectly developed, the ventral spinal roots were slender, the number of their fibers reduced and the myelin defective. The great motor ganglion cells of the anterior horns were reduced in number and size and were abnormally angular and irregular in shape.

Baudouin also has described hypertrophic in addition to atrophic fibers, proliferation of the connective tissue, multiplication of sarcoplasma nuclei and indistinct transverse striation. These changes, however, were of minor degree. The nervous system revealed profound alterations. The size and perhaps also the number of the cells of the anterior horns, was diminshed; in the various nerve trunks many axis-cylinders were without myelin; the nuclei of the sixth and twelfth cranial nerves showed chromatolysis. Baudouin ascribed the condition to a retarded myelination of the nerves and an inhibition of the development of the cells of the anterior horns.

Rothmann's case presented even more extreme lesions. In addition to extensive atrophy of the great motor cells throughout the anterior horns of the cord were also alterations of the white substance and a diminution in number of the cells of Clark's columns. The smallness of the cord was striking. The motor ganglion cells of the hypoglossus nucleus were numerically decreased and showed chromatolysis. The

peripheral nerves were partly thickened, owing to enlarged septa of connective tissue, with multiplication of the nuclei. The transverse diameters of the nerve filaments were reduced, the single fibers were also very slender, though not changed in number or structure, and pursued a wavy course. The principal changes in the muscles consisted in pronounced proliferation of the intermuscular connective tissue, in abundant small cellular proliferation and marked development of fatty tissue between the muscle fibers, which last had partly disappeared.

Likewise Kaumheimer at postmortem in his case found, in addition to muscular changes, profound alterations of the nervous system. There were signs of severe degeneration of the peripheral nerves: marked diminution in number of the fibers, corresponding proliferation of the perineural and endoneural connective tissue and a marked increase of Schwann's nuclei. Many of the remaining fibers were small and of varying diameter; some showed a wavy course in longitudinal cuts. In various places the myelin sheaths and the axis cylinders were absent, though no marrowless axis cylinders could be detected.

The central nervous system showed extensive alterations, most pronounced in the motor cell columns of the spinal cord and in the medulla oblongata. There was proliferation of the glia in the marrow of the brain hemispheres, in the medulla oblongata and in the white substance of the spinal cord; atrophy in the nucleus of the hypoglossus nerve, in Clark's columns and the anterior horns of the entire spinal cord.

NATURE OF THE DISEASE

The views concerning the nature of the disease vary, inasmuch as many difficulties arise in the interpretation of the various pathologic changes.

Before any pathologic examinations were on record, Oppenheim regarded the disease as a retardation of development of the muscles, a conclusion later supported by Spiller, who failed to discover either gross or minute changes in the nervous system. Oppenheim, however, considered also the possibility of retarded development of certain nerve centers and their function, especially of the anterior horns of the spinal cord.

The findings of subsequent authors demonstrated indeed that the whole peripheral neuron may be affected, different segments varying in degree in different cases. If we remember that the ganglia cells of the spinal cord, the peripheral nerves and the muscle constitute a physiologic unit, this is not surprising.

The muscle findings place the affection near the group of the so-called primary myopathias—dystrophia musculorum progressiva. But while in myatonia the lesions extend to the nervous system in the majority of cases so far reported and are only exceptionally limited to the muscles, on the contrary, in dystrophy we observe, as a rule, muscular alterations alone, such as atrophy, hypertrophy of the fibers, multiplication of the muscle nuclei, etc., though in exceptional cases—those of long duration especially—degenerative alterations of the nerve elements were also found, these perhaps being secondary. (Transitional cases of Heubner, Struempell, Preis.)

On the other hand, since in primary spinal atrophies combinations with pseudohypertrophy of muscles also are known, the anatomic demarcation between myelopathic (spinal) and myopathic atrophies becomes still less sharp; though it must be admitted, that the hypertrophic fibers observed for instance in poliomyelitis acuta or in neurotic muscular atrophy were apparently present only in small number. All this tends to demonstrate the possibility of a relationship between primary dystrophy and spinal muscular atrophy.

A number of authors hold myatonia as at least a process closely related to muscular dystrophy, if not a congenital form of this disease. Jendrassik thinks that the possibility of improvement in myatonia as opposed to dystrophy forms no essential difference in the nature of these affections; for he considers in myatonia the clinical improvement not to be a real (anatomic) restoration but rather an improvement of the innervation of individual muscles or muscle fibers originally less affected. At present clinical evidence does not permit us to classify myatonia as progressive dystrophia musculorum. Also the frequency and degree of peripheral nerve and spinal cord alterations in myatonia evidence dissimilarity from dystrophy, and suggest a relationship to the spinal atrophies.

The possibility of the existence of primary lesions in the muscles in at least a number of cases will not be denied in the presence of such findings as Spiller reports though indeed the theory is permissible that in such cases the original minor affection of the motor ganglia cells was not irreparable, and for this reason the ganglia cells in the later stage of the process failed to show the former lesions. On the other hand, such a degree of lesions of the nervous system as quoted above seems almost to exclude the probability of anatomic restitution; and in view of my own findings I am inclined to attribute the clinical improvement in my case more to amelioration of the function than to a progressive anatomic development.

Rothmann calls attention to the great similarity of his findings in myatonia to those of Wernig-Hoffmann's spinal infantile atrophy of

the muscles, and also emphasizes that the clinical differences are not always marked, as cases of Wernig-Hoffmann's atrophy without family grouping are known, and, on the other hand, myatonia has been found among several members of the same family. (Sevestre, Collier-Wilson, Sorgente). Rothmann unites both forms in one group of spinal atrophies in spite of the clinical fact that myatonia is congenital and not progressive (with rare exceptions), whilst Wernig-Hoffmann's atrophy usually begins in the second or third semester of life. He thus distinguishes a congenital and an early infantile form which show no sharp line of demarcation. In his opinion, improvement in cases indicates that they should be regarded as of myatonia, while progressive cases belong to the Wernig-Hoffmann type of the disease.

He excludes fetal poliomyelitis in his case. Marchi specimens proved to him the fetal origin of the disease and that the degenerative processes were continued during the first months of life. He considers that agenesy of the ganglion cells is improbable.

As to the assumption that the disease shows a relationship to Moebius' infantile *Kernschwund* no verdict can be given at present; theoretically the possibility must be admitted that an affection does exist in which the cells of the anterior horns are aplastic or defective, a condition of similar nature to that shown in Moebius' *Kernschwund;* so that their function is either absent or is only present after a period of inactivity.

A resistentia minor of the protoneuron may be possible in all these affections owing to developmental inferiority, which is only temporary in some cases and to a certain extent reparable (myatonia), but which in others is progressive and lethal (spinal muscular atrophy).

Kaumheimer concludes from the histologic examination in his case that myatonia must be considered as either a toxic or endogenic affection; the theory that the pathologic basis of this disease lies in inhibition of development or inflammatory processes should be discarded. The process is not necessarily complete at birth, as alterations of the muscles may result even months later.

Berti suggested from his study of his own and other reported cases that a relationship exists between myatonia and subcretinism or submyxedema; and Cattaneo and Silvestri likewise believe the disease to be due to a disturbance of some internal secretion. The sclerotic changes of the thymus noted by Spiller-Smith and the sclerosis of the spleen, thyroid gland and thymus observed in Baudouin's case seemed to support these views. In Rothmann's case the thymus was enlarged, Hassal's corpuscles being strongly developed; though he did not regard this as important. Other authors, as Collier-Holmes, Lereboullet-Baudouin and Rothmann could find no changes in these organs, so that

these isolated positive findings hardly offer a sufficient basis for broad conclusions. The improvement which occurred in Silvestri's case on adrenalin administration and in Lepine's case after thyroid therapy, may have been accidental since Oppenheim's disease has a tendency toward spontaneous improvement.

Though our experience concerning the function of the thymus so far does not establish its relationship to the muscle and nervous lesions seen in Oppenheim's disease, we know, nevertheless, that thymectomy in animals causes myasthenia with certain neuromuscular alterations in addition to the well-known skeletal changes. These are, simple atrophy with transition to degenerative atrophy in the muscles, marked reduction in the caliber of the fibers, partial loss of the transverse striation, multiplication of the sarcolemmal nuclei and the nuclei of the internal perimysium, and distinct proliferation of the interfascicular connective tissue with formation of adipose tissue.

These results of animal experiments possess interest also in connection with the muscular lesions in man, found in myasthenia gravis and myasthenia pseudoparalytica with persistence of the thymus, and in connection with the degenerative changes of the muscles seen in disturbances of various other endocrine glands, as in Basedow's disease.

According to Biedl examination of the nervous system of thymectomized animals revealed only minor alterations in the peripheral nerves and slight degenerative conditions in the spinal cord. The myelin sheaths in the cord showed disintegration, the ganglion cells of the gray matter were swollen, lighter stained, with indistinct protoplasm and changes of the nuclei, indicating also a beginning disintegration in them. These observations although for our problem merely suggestive and of only speculative service, should induce us nevertheless to direct careful attention to the organs of internal secretion at necropsies in future in cases of Oppenheim's disease.

At present the morbid agent in the spinal and muscular changes, the cause of Oppenheim's myatonia in the fetus is not known, nor do the findings allow an undisputed classification of the disease.

MUSCULAR LESIONS IN RACHITIC MYOPATHY

It may not be amiss to call attention here to affections of the muscular system demonstrated in such general diseases as rachitis. This rachitic myopathy is considered a primary, specific and co-ordinate to the alterations of the skeleton; it bears a certain clinical resemblance to myatonia congenita. The morphologic changes found in the texture of the muscles in the clinically pronounced hypotonia and pseudoparesis of rachitic babies were marked reduction of the caliber of the

fibers, defective transversal striation, marked longitudinal striation, striking increase in the number of the muscle nuclei, lack of fatty tissue, indistinct sarcolemmal edges and densely crowded fibers, conditions different from those seen in Oppenheim's disease.

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